

ABNORMALLY FLAT FACIAL PROFILE ON TWO- AND THREE-DIMENSIONAL ULTRASOUND AND ARRAY COMPARATIVE GENOMIC HYBRIDIZATION FOR THE DIAGNOSIS OF PALLISTER-KILLIAN SYNDROME

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A 40-year-old, gravida 2, para 1, woman underwent amniocentesis at 16 weeks of gestation because of advanced maternal age. Her husband was 43 years of age. Both parents were healthy, and there was no family history of congenital malformations. Amniocentesis revealed mosaicism for a supernumerary isochromosome consisting of two entire short arms of chromosome 12 or i(12)(p10). The karyotype was 47,XX,+i(12p)[16]/46,XX[9] derived from 25 colonies of amniocytes, with 64% (16/25) of the amniocytes being +i(12p). The parental karyotypes were normal. Prenatal ultrasound at 19⁺⁴ weeks of gestation revealed a normal volume of amniotic fluid, macrocephaly with a biparietal diameter of 5.01 cm (21.72 weeks), hypertelorism, an abdominal circumference of 15.27 cm (20.48 weeks), a femur length of 3 cm (19.26 weeks), and a flat face with a very small nose and protruding lips (Figures 1 and 2). A diagnosis of Pallister-Killian syndrome (PKS) was made. The pregnancy was subsequently terminated, and a 399-g fetus, with macrocephaly, a large coarse face, a long philtrum, retrognathia, a Cupid's bow mouth with thin lips, a flattened nose with a low nasal bridge, anteverted nostrils, upslanting palpebral fissures and low-set ears, was delivered (Figures 3 and 4). Postnatal



Figure 1. Two-dimensional ultrasound at 19 weeks of gestation showing relative macrocephaly and a flat face with a very small nose and protruding lips.

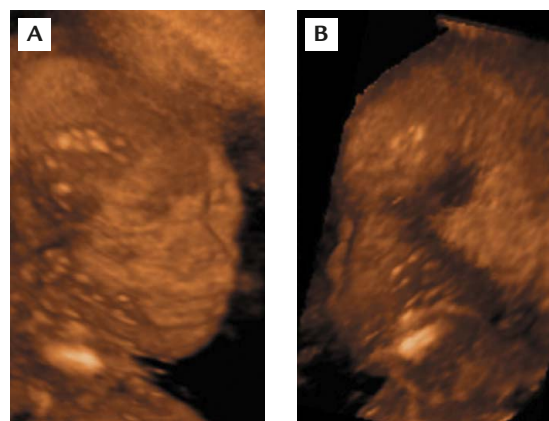


Figure 2. (A) Anterior and (B) lateral craniofacial appearance on three-dimensional ultrasound at 19 weeks of gestation showing a large coarse face, a flattened nose with a low nasal bridge, anteverted nostrils, and protruding lips.



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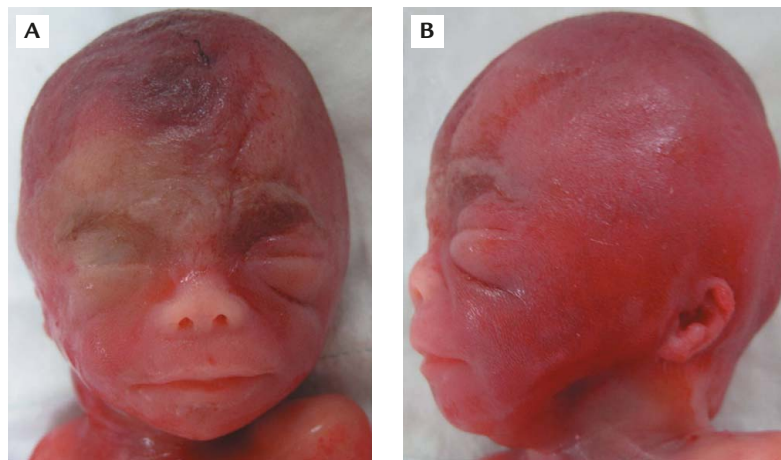


Figure 3. (A, B) Corresponding craniofacial appearance of the fetus at birth.



Figure 4. Whole body view of the fetus with relative macrocephaly.

cytogenetic analysis of the fetal skin confirmed the pre-natal diagnosis. The umbilical cord had a 47,XX,+i(12p) karyotype (Figure 5). Array comparative genomic hybridization (aCGH) using genomic DNA extracted from the umbilical cord showed a copy number gain for all clones spanning the short arm of chromosome 12 (Figures 6 and 7).

PKS (OMIM 601803) was first described by Pallister et al [1], Teschler-Nicola and Killian [2] and Killian et al [3]. It is a dysmorphic condition caused by mosaicism of a supernumerary tissue-limited isochromosome 12p [i(12p)] or mosaic tetrasomy 12p. PKS is characterized by mental retardation, seizures, pigmentary skin lesions, temporofrontal balding or sparseness with abundant hair over the top of the head (giving a pattern like that of Iroquois Indians), hypertelorism, a short nose with anteverted nostrils, a flat nasal bridge, a short neck, and flat occiput [4]. The mosaic level of i(12p) in lymphocytes and fibroblasts does not correlate with the

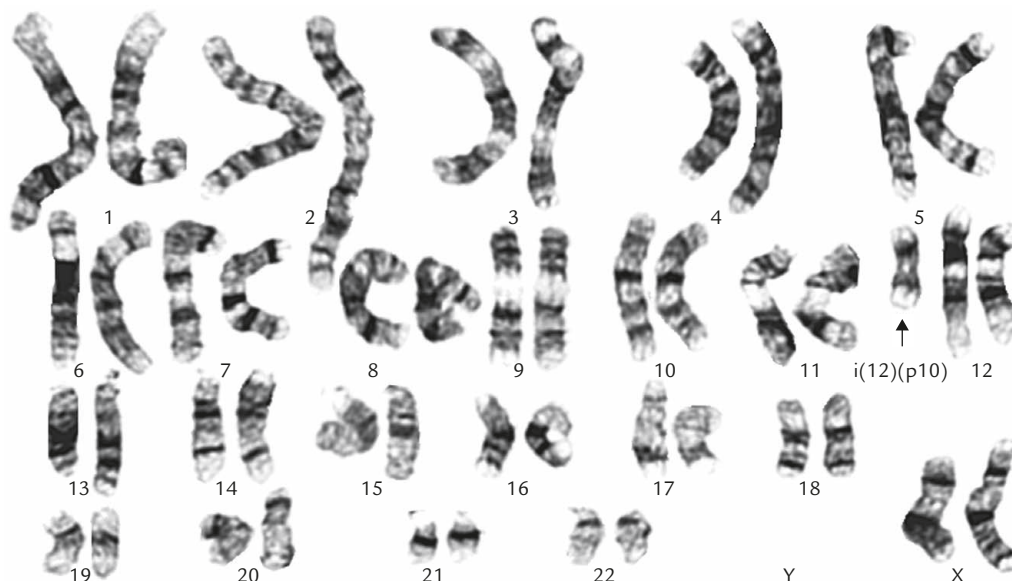


Figure 5. A 47,XX,+i(12)(p10) karyotype. The arrow indicates a supernumerary isochromosome 12p [i(12p)].

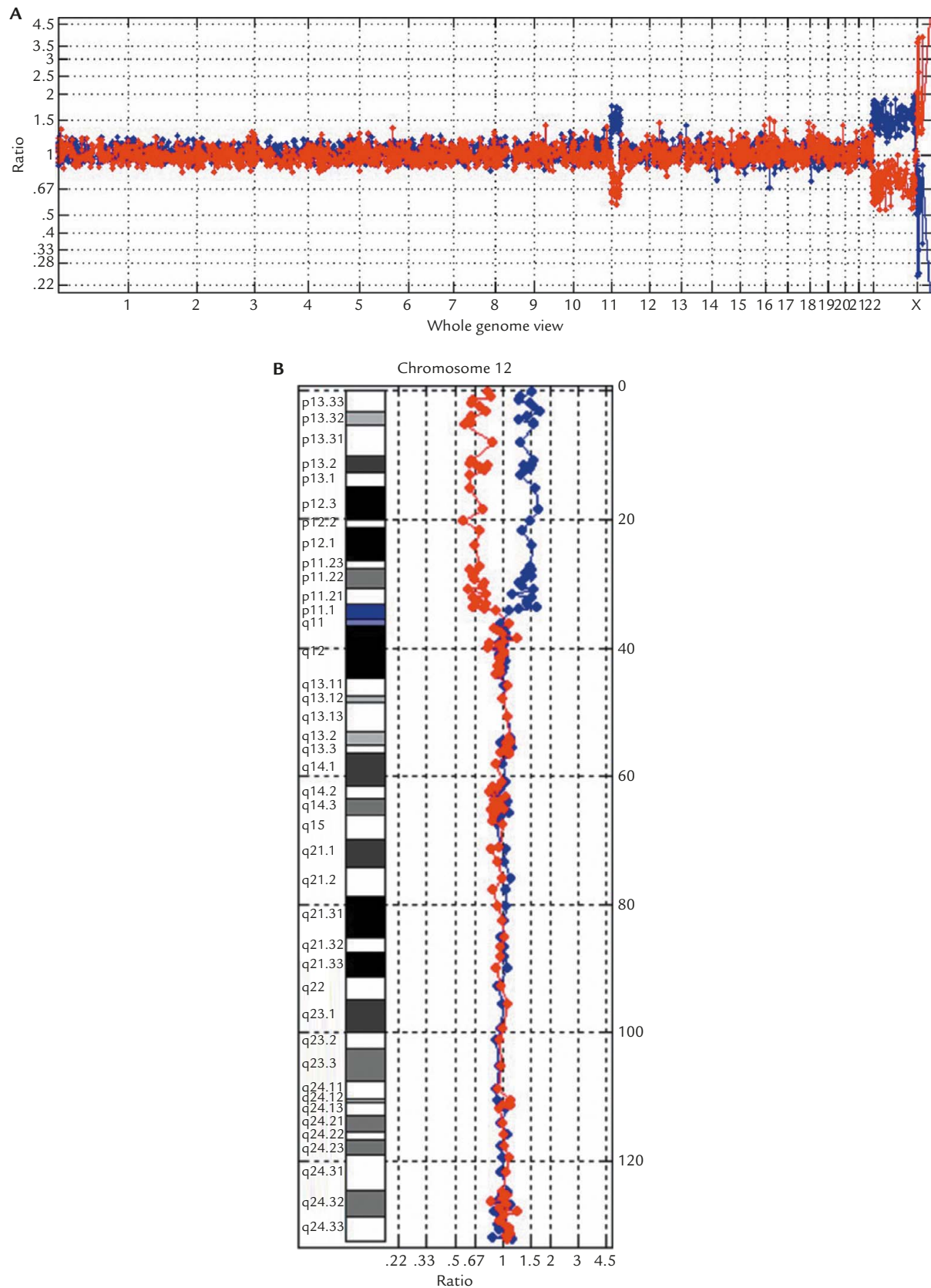


Figure 6. Bacterial artificial chromosome-based array comparative genomic hybridization analysis (CMDX, Irvine, CA, USA) bacterial artificial chromosome array comparative genomic hybridization CA3000 chips showed a copy number gain for all clones on 12p13.33–p11.1 (RP11-283I3 → RP11-747M3).

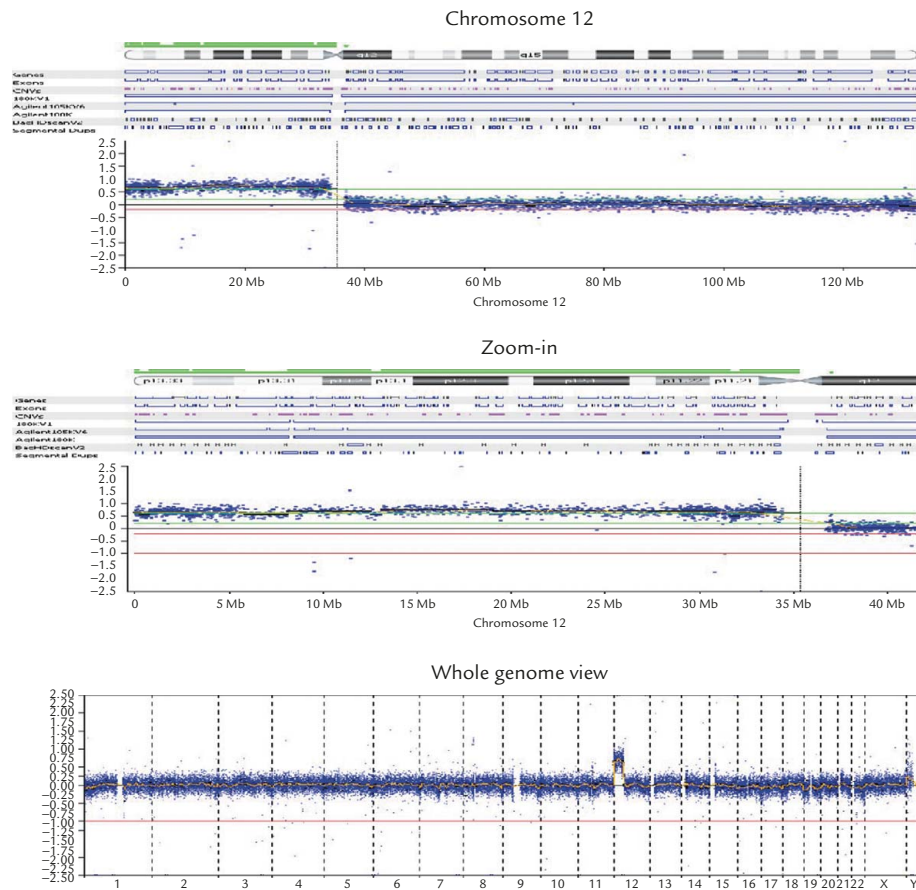


Figure 7. Oligonucleotide-based array comparative genomic hybridization analysis using Oligo HD Scan (CMDX, Irvine, CA, USA) showing a 35.4-Mb duplication (0–35,400,000 bp) of the short arm of chromosome 12.

severity of the phenotype [4,5]. Reported prenatal sonographic features of PKS include congenital diaphragmatic hernia, polyhydramnios, abnormal extremities, increased nuchal translucency, nuchal edema, cystic hygroma, cardiovascular anomalies, central nervous system anomalies, an abnormal flat facial profile, and other abnormalities such as omphalocele, hydrops fetalis, macrosomia, intrauterine fetal growth restriction, hydronephrosis, hypoplastic stomach, ambiguous genitalia, echogenic bowel and single umbilical artery [6].

The present case had prenatal sonographic findings of relative macrocephaly, hypertelorism, a flat face, a small nasal bridge, anteverted nostrils, protruding lips, and low-set ears. An abnormally flat facial profile on two-dimensional (2D) and three-dimensional ultrasound should alert physicians to PKS and prompt cytogenetic investigations for mosaic tetrasomy 12p. Paladini et al [7] reported 2D ultrasound diagnosis of an abnormal flat facial profile with a small nose, a protruding lower lip and low-set ears at 21 weeks of gestation in a fetus with PKS, diaphragmatic hernia and rhizomelic limb shortening. Liberati et al [8] reported 2D ultrasound diagnosis of an abnormal flat facial

profile with a very small nose and protruding lips at 23 weeks of gestation in a fetus with PKS, diaphragmatic hernia, polyhydramnios, rhizomelic micromelia, macrocephaly, increased nuchal thickness, bilateral club foot, and macrosomia. Sananes et al [9] reported three-dimensional ultrasound diagnosis of mild retrognathia and a very long philtrum at 26 weeks of gestation in a fetus with PKS and polyhydramnios. Paladini et al [7] suggested that a detailed ultrasound assessment of the fetal face may significantly contribute to the direct diagnosis of PKS and aid differentiation between PKS and Fryns syndrome.

aCGH allowed rapid confirmation of PKS in the current case. aCGH can provide rapid genome-wide analysis without the need for cell cultures. PKS is cytogenetically characterized by tissue-limited or tissue-specific mosaicism. In cases of PKS, mosaic tetrasomy 12p may be misdiagnosed as mosaic tetrasomy 21 based on traditional G-banded analysis [10–12]. Priest et al [13] suggested that tetrasomy 12p cells were less stable in blood lymphocyte and amniocyte cultures than in fibroblast-like cultures derived from skin and other tissues, and that young cultures at early passage were more

likely to have tetrasomy 12p than old cultures. Polityko et al [14] observed a decrease in the number of abnormal amniocyte clones with tetrasomy 12p cells in the PKS fetus. Chen et al [15] reported cytogenetic variability in the proportion of abnormal cells between the various tissues in prenatally detected mosaic tetrasomy 12p. aCGH based on genomic DNA extracted from uncultured blood cells was recently used to show a gain of the entire short arm of chromosome 12 in patients with PKS [16,17]. Our case demonstrates the usefulness of aCGH using genomic DNA from extra-embryonic tissues for the identification of PKS.

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